REMARKS

35 U.S.C. § 101

Claims 27-34 remain rejected under 35 U.S.C. § 101 as allegedly not being supported by a substantial utility. In particular, while acknowledging that "the Examiner does not dispute that the asserted utility is credible," the Office action argues that "the assertion that the polypeptide can be used diagnostically is not considered a substantial utility." (Page 8 of the Office action mailed 9/20/05).

Applicants respectfully disagree. A "substantial utility" is defined as:

> a utility that defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measure or further monitoring.

Revised Interim Utility Guidelines Training Materials, pg. 6. The diagnostic utility of the PRO347 polypeptide, asserted at least at page 137 of the specification, is a substantial utility because it is based on a correlation between the gene amplification demonstrated in Example 28 of the present specification and protein overexpression in lung and breast cancer tissues. Although the claimed PRO347 polypeptide might not provide an "immediate benefit" to the public, that is not the standard. Indeed, according to Section 2107 of the MPEP:

> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulation in other cases to meant that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

Applicants respectfully submit that the diagnostic utility of the PRO347 polypeptide is both reasonable and provides a public benefit. Indeed, Applicants have previously explained that based on the correlation between gene amplification levels and protein overexpression, and based on the fact that the PRO347 nucleic acid is amplified in lung and colon tumors, the PRO347 polypeptide may be used diagnostically to determine whether a breast or lung tissue sample likely is cancerous. Furthermore, Applicants also have explained, and provided declaratory evidence demonstrating that even if amplification of the PRO347 gene does not correlate with overexpression of the PRO347 polypeptide, which Applicants expressly do not concede, the PRO347 polypeptide still is useful because simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor. Thus, Applicants respectfully maintain that the claimed PRO347 polypeptide provides a "public benefit" and is supported by at least one substantial utility.

In maintaining rejection of Claims 27-34 for alleged lack of utility, Applicants respectfully maintain that the Office applies an improper legal standard. Indeed, all that is required is that the Applicant shows that the totality of the evidence demonstrates that the Office has NOT established that it is more likely than not that one of ordinary skill in the art would doubt that mRNA expression levels correlate with protein expression levels. *See In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Applicants respectfully maintain that when the evidence is considered in its totality, as it must be, it is clear that more likely than not, one of ordinary skill in the art would find the diagnostic utility asserted by Applicants to be a "substantial" utility.

The Office action argues that this utility is not substantial because according to the Office, "one skilled in the art would not assume that an increase in gene copy number would correspond with an increase in mRNA levels or protein levels without doing the empirical experimentation necessary to measure mRNA and protein levels. The requirement for such empirical experimentation indicates that the asserted utility for the

claimed polypeptides is not substantial; it is not in currently available form." (Page 8 of the Office action mailed 9/20/05). In support, the Office relies on references by Haynes, Gygi, Pennica, Chen, and Anderson. As previously argued in the response submitted December 24, 2003, the Haynes and Gygi references are not persuasive because the results discussed in those references were not obtained in a human system, did not examine any particular human gene or protein expression, and most significantly, did not examine any genes that are amplified in a cancerous state. Instead, Haynes and Gygi both examine the ability to predict protein expression levels in a biological *system.* Specifically, Haynes and Gygi examine whether there is an *overall system* correlation between gene and protein expression levels. *See* Haynes, *et al.,* "Proteome analysis: Biological assay or data archive?" *Electrophoresis,* 1998. 19:1862-1871, 1863; Gygi *et al.,* "Correlation between Protein and mRNA Abundance in Yeast," *Molecular and Cellular Biology.* 1999. 19(3): 1720-1730, 1720.

Further, as also as previously argued, even if Haynes and Gygi were a comparable system, both report that "[f]or the entire group (106 genes) for which a complete data set was generated, there was a general trend of increased protein levels resulting from increased mRNA levels." Gygi *et al.,* at 1726; Haynes *et al.,* 1863. In fact, Gygi reports that the Pearson product moment correlation coefficient for the whole data set was 0.935. Gygi *et al.,* at 1726. Thus, neither the Haynes nor the Gygi reference makes it more likely than not that one of ordinary skill in the art would find the diagnostic utility asserted by Applicants to be not substantial.

Applicants also previously explained that the Pennica reference does not demonstrate that more likely than not one of ordinary skill in the art would doubt Applicants' assertion of a diagnostic utility. In particular, Pennica examines whether there is correlation between gene amplification and protein overexpression for 3 *wisp* genes. As discussed in the Amendment and Response submitted December 24, 2003, Pennica explains that *WISP-1* gene amplification and RNA expression levels showed a significant positive correlation. In addition, although *WISP-3* was not significantly amplified, it was amplified (P=1.666) and significantly overexpressed. Further, although *WISP-2* gene

amplification and RNA expression levels seemed to be inversely related, Pennica *et al.* state that this result might be inaccurate. Specifically, Pennica *et al.* suggest that "[b]ecause the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." *See* Pennica *et al.,* "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1 transformed cells and aberrantly expressed in human colon tumors," *PNAS.* 1998. 95:14717-14722, 14722. Therefore, the Pennica reference also does not make it more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of a diagnostic utility.

Additionally, although the Chen reference cited by the Examiner examines correlation between gene amplification and protein overexpression in human lung adenocarcinomas, the teachings of Chen do not make it more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility. Indeed, Chen "*suggests* that it is not possible to predict *overall* protein expression levels based on *average* mRNA abundance in lung cancer samples." Chen *et al.,* "Discordant Protein and mRNA Expression in Lung Adenocarcinomas," *Mol.& Cellular Proteomics 1.4.* 2002. 304-313, 311-12. However, Applicants assertion of utility is not based on *overall* protein expression levels or *average* mRNA abundance in lung cancer samples. Rather, Applicants assertion is based on the gene amplification demonstrated and measured in Example 28 of the specification. It is correlation between this specific gene amplification and protein overexpression of the specific PRO347 polypeptide, encoded by the PRO347 gene that is amplified, upon which Applicants base their assertion of a diagnostic utility. *See e.g.* the Polakis Declaration, submitted herewith and discussed more fully below (providing declaratory evidence that when gene amplification as described in Example 28 of the specification was observed in the Tumor Antigen Project, a project which led to the development of the PRO347 molecules, 80% of the time the gene amplification was found to correlate with a change in gene-product (*i.e.* protein) expression levels).

The Office action cites another reference, Anderson *et al., Electrophoresis,* Vol. 18, pages 533-537 (1997), and alleges that Anderson "found that there was a poor correlation (0.48) between mRNA and protein levels in liver cells (abstract, page 535). They suggest that the two major phases of gene expression regulation (transcription through message degradation on the one hand, and translation through protein degradation on the other) are of approximately equal importance in determining the net output of proteins." (Page 7 of the Office action mailed 9/20/05). Although the Anderson reference examines whether there is correlation between mRNA and protein expression levels in a *human* sample, the teachings of Anderson do not make it more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility. In particular, the Anderson reference does not teach that no correlation was observed but rather teaches that almost fifty percent of the time correlation was observed and almost fifty of the time correlation was not observed. This is not evidence that weighs heavily in favor of finding that one of skill in the art would *more likely than not* doubt the truth of Applicants' assertion of utility. Furthermore, the Anderson reference is not persuasive because it does not examine a *diseased* human system, such as breast or lung cancer, nor does Anderson examine whether a gene that is amplified in a diseased system correlates with overexpression of the encoded protein in that diseased system.

In addition, even if Anderson teaches that transcription and translation are equally important in determining a correlation between gene and protein expression levels, Applicants have submitted ample evidence demonstrating a correlation between gene amplification, mRNA expression levels, and protein overexpression. In particular, as explained in the Amendment and Response submitted December 24, 2004, the Pollack, Hyman, and Varis references relied on by Applicants demonstrate correlation between gene amplification and mRNA levels. In addition, the Bermont, Orntoft, and two Hu references, discussed in both the Response submitted December 24, 2004 and the Response submitted July 8, 2005, demonstrate correlation between mRNA and protein expression levels. Indeed, taken in total, the articles by Pollack, Hyman, Varis, Bermont, Orntoft, and Hu (made of record in Applicants' Responses mailed 24

December 2004 and 8 July 2005) collectively teach that in general, gene amplification increases mRNA expression and correlates with protein overexpression.

The Office action rejects the Pollack, Hyman, Varis, Bermont, Orntoft, and Hu references relied on by Applicants, stating that those reference only report on single genes or small sample sizes. The Office action argues that Haynes, Gygi and Chen used much larger sample sizes. However, as discussed above, Haynes and Gygi do not examine any human, diseased population. Rather, those references discuss whether a correlation is observed in yeast populations. Furthermore, even if the yeast system discussed in Haynes and Gygi were comparable to the diseased human system in which PRO347 is expressed, as discussed above, Haynes and Gygi report that "[f]or the entire group (106 genes) for which a complete data set was generated, there was a *general trend of increased protein levels resulting from increased mRNA levels*." Gygi *et al.,* at 1726 (emphasis added); Haynes *et al.,* 1863. Thus, in the larger system, a correlation was observed. In addition, the Orntoft article relied on by Applicants examined 40 well-resolved and focused proteins and found a correlation between gene amplification and protein overexpression in a similar system, human bladder cancer. The sample size in Orntoft is nearly twice the sample size (23 proteins) examined in the Anderson reference relied on by the Examiner. Thus the teachings in the references relied on by the Examiner, Hyman, Gygi, Chen and Anderson, do not outweigh the teachings in the references relied on by Applicants, *i.e.* Pollack, Hyman, Varis, Bermont, Orntoft, and Hu. Nor do the references relied on by the Examiner make it more likely than not that one of ordinary skill in the art would doubt Applicants assertion that the PRO347 polypeptide has a diagnostic utility.

In addition, the Office also must consider the significant declaratory evidence relied on by Applicants. Specifically, in addition to the Pollack, Hyman, Varis, Bermont, Orntoft, and Hu references, Applicants have submitted significant declaratory evidence demonstrating that the claimed PRO347 polypeptide is supported by a substantial diagnostic utility. According to MPEP § 2107, the Examiner must accept an opinion

from a qualified expert and should not disregard the opinion "solely because of a disagreement over the significance or meaning of the facts offered."

First, Applicants previously submitted with their Response mailed June 24, 2003, the Declaration of Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold in a tumor sample relative to a normal sample by the gene amplification assay discussed at pages 119-137 of the present application, is useful as a marker for the diagnosis of cancer. As previously argued, at page 137 of the specification, Applicants assert that the claimed PRO347 polypeptide is useful as a diagnostic marker because the PRO347 polypeptide is encoded by a nucleic acid that is amplified in lung and colon tumors. (*See e.g.* Example 28, pages 119-137 of the specification). Indeed, the specification discloses that the gene encoding the PRO347 polypeptide showed significant amplification, ranging from 2-fold to nearly 8-fold in 38 different lung and colon primary tumors and tumor cell lines, a majority of those tumors and cell lines tested.

In addition, Applicants herein submit a declaration of Paul Polakis, Ph.D., principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. Dr. Polakis declares that in general, there is a correlation between mRNA levels and polypeptide levels. More specifically, Dr. Polakis explains:

> 4. In the course of the research conducted by Genentech's Tumor Antigen Project . . . using mircroarray analysis, we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed.
>
> 5. From the mRNA and protein expression analyses described in paragraph 4 above, we have observed that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of

protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells.

6. Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

Significantly, Dr. Polakis declares that "in approximately 80%" of the cases observed in connection with the Tumor Antigen Project, increases in the mRNA levels correlated with changes in the levels of protein expression. Thus, this is direct evidence of the empirical experimentation the Office action asserts would be necessary for one in the art to accept that gene amplification correlates with protein overexpression. Indeed, as stated above, according to MPEP § 2107, the Examiner "must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." (emphasis added).

Applicants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars of sales in their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.*, that it is more likely than not informative of the protein level).

Thus, when the evidence discussed above is considered in totality, although there are some examples in the scientific art, such as those disclosed by Chen *et al.*, that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the

rule. In the majority of amplified genes, as exemplified by Orntoft *et al.,* Hyman *et al,* Pollack *et al,* Varis *et al.,* Bermont *et al.,* Hu *et al.,* and the Goddard and Polakis Declarations, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels.

When considered in totality, as the evidence must be, MPEP § 2107, even in combination, the Pennica, Haynes, Gygi, Chen and Anderson references, do not outweigh the teachings exemplified by Orntoft *et al.,* Hyman *et al,* Pollack *et al,* Varis *et al.,* Bermont *et al.,* Hu *et al.,* and the Goddard and Polakis Declarations. "Only when the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained." MPEP § 2107 (emphasis added). Thus, Applicants respectfully submit that in view of the substantial evidence discussed above, the maintained rejection of claims 27-34 for alleged lack of utility is improper.

Moreover, Applicants submit that even if there is no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Applicants submit that as evidenced by the Ashkenazi Declaration (submitted with Applicants' Response mailed 24 December 2003), and the teachings of Hanna and Mornin (Pathology Associates Medical Laboratories, August (1999), attached herewith), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor as demonstrated by the real-world example of the breast cancer marker HER-2/neu. This is a substantial utility adequate to satisfy the utility requirement of 35 U.S.C. § 101. Indeed, according to § 2107 of the MPEP, "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

For all these reasons, Applicants maintain that rejection of claims 27-34 for alleged lack of utility is improper. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

35 U.S.C. § 112 ¶ 1, Enablement-Utility

Claims 27-34 stand rejected under 35 U.S.C. § 112 ¶1, because it is alleged that the presently claimed invention is not supported by a substantial utility, and therefore, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, addressing the rejection under 35 U.S.C. § 101 for lack of utility, Applicants respectfully submit that the claimed polypeptide is supported by a substantial utility. Thus, Applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

SUMMARY

Applicants believe that currently pending Claims 27-34 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

C. Noel Kaman

C. Noel Kaman
Registration No. 51,857
Attorney for Applicant

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200